

Applicants : Hilton A. Salhanick and Joachim Hourihan
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Office Action have been overcome, and respectfully request that the Examiner reconsider and withdraw same.

The Claimed Invention

This invention relates to a method of diagnosing a thyroid condition in a subject. This method comprises obtaining a suitable urine sample from the subject, determining the concentration of thyroid stimulating hormone (TSH) in the sample by a method which is not a radioimmunoassay and comparing the concentration of TSH with a urinary concentration of TSH in a normal subject, wherein (i) a concentration of TSH which is higher than the urinary concentration of TSH in the normal subject diagnoses hypothyroidism in the subject and (ii) a concentration of TSH which is lower than the urinary concentration of TSH in the normal subject diagnoses hyperthyroidism in the subject.

This invention is based on applicants' *surprising* discovery that measuring urinary TSH is a reliable screening procedure for detecting hypothyroidism and hyperthyroidism.

Rejections Under 35 U.S.C. §112, Second Paragraph

The Examiner rejected claims 94-101 and 110-122 under 35 U.S.C. §112, second paragraph, as being allegedly indefinite for failing to point out and distinctly claim the subject matter which applicants regard as the invention.

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The Examiner asserted that claims 94 and 110 are vague and indefinite as to what kind of sample is considered "suitable."

In response, applicants respectfully traverse the Examiner's rejection.

According to the Merriam-Webster OnLine dictionary (<http://www.m-w.com>), a printout of which is annexed hereto as Exhibit A), the term "suitable" means "adapted to a use or purpose." Furthermore, applicants direct the Examiner's attention to the instant specification; specifically, page 47, line 33 through page 48, line 6, and page 48, lines 16-19, as exemplifying types of urine samples suitable for their stated purpose. That is, the specification lists suitable urine samples as including, for example, unconcentrated urine, urine concentrated by centrifugation, precipitation or filtration, and urine modified via pH adjustment and dilution.

The Examiner also asserted that claims 94 and 110 are vague and indefinite because it is unclear as to what method "a method which is not a radioimmunoassay" refers.

In response, applicants respectfully traverse the Examiner's rejection.

Again, applicants direct the Examiner to the specification at, *inter alia*, page 48, lines 20-25, for a list comprising methods of determining the concentration of TSH in a sample, which methods are not radioimmunoassays. Such non-radioimmunoassay methods include, for example, "fluorescence, polarized

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fluorescence, turbidity, chemiluminescence, agglutination and methods of antigen-antibody reaction."

In view of the above remarks, applicants maintain that claims 94-101 and 110-122 satisfy the requirements of 35 U.S.C. §112, second paragraph.

Rejections Under 35 U.S.C. §103(a)

The Examiner rejected claims 94-101, 132 and 133 under 35 U.S.C. §103(a) as allegedly unpatentable over Kuku, et al. (Journal of Endocrinology, 1974, Vol. 62, pages 645-655), in view of Shuurs, et al. (U.S. Patent No. 4,016,043).

In response to the Examiner's rejection, applicants respectfully traverse, and maintain that the Examiner has failed to establish a *prima facie* case of obviousness.

To establish a *prima facie* case of obviousness, the Examiner must demonstrate three things with respect to each claim. First, the cited references, when combined, must teach or suggest every element of the claims. Second, one of ordinary skill must have been motivated to combine the teachings of the cited references at the time of the invention. Third, there must have been a reasonable expectation that the claimed invention would succeed.

Here, the cited references fail to support a *prima facie* case of obviousness. Specifically, to support a *prima facie* case of obviousness, Kuku, et al. and Shuurs, et al., combined, would

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have to teach or suggest every element of the claims.

Kuku, et al. and Shuurs, et al. do not do this.

Claims 94-101, 132 and 133 are discussed above. Briefly, these claims provide a method of diagnosing a thyroid condition in a subject which comprises obtaining a suitable urine sample from the subject, determining the concentration of TSH in the sample by a method which is not a radioimmunoassay and comparing the concentration of TSH with a urinary concentration of TSH in a normal subject, wherein (i) a concentration of TSH which is higher than the urinary concentration of TSH in the normal subject diagnoses hypothyroidism in the subject and (ii) a concentration of TSH which is lower than the urinary concentration of TSH in the normal subject diagnoses hyperthyroidism in the subject.

Kuku, et al. teach measurement of urinary excretion rates of exogenously added (i.e., by intravenous pre-injection), ¹³¹I-labelled, purified human pituitary TSH in normal patients, as well as those with evidence of hypo- and hyperthyroidism, by double antibody radioimmunoassay after concentration of the urine by dialysis followed by lyophilization.

Kuku, et al. do not teach the diagnosis of a thyroid condition in a subject which comprises obtaining a suitable urine sample from the subject, determining the concentration of TSH in the sample by a method which is not a radioimmunoassay and comparing the concentration of TSH with a urinary concentration of TSH in a normal subject in order to diagnose hypothyroidism or

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hyperthyroidism in the subject.

Furthermore, the measurements of TSH provided in Kuku, et al. (see page 652) are excretion rates, which are measured in $\mu\text{U/hr}$. Thus, contrary to the assertion by the Examiner, these excretion rates cannot properly be compared to applicants' claimed TSH ranges measured in $\mu\text{IU/ml}$.

The deficiencies of Kuku, et al. are not cured by Shuurs, et al. Shuurs, et al. teach an enzyme immunoassay (EIA) test system especially adapted for the detection and determination of a component of an antigen-antibody reaction.

Shuurs, et al. do not teach or suggest the diagnosis of a thyroid condition in a subject, especially one which comprises obtaining a suitable urine sample from the subject. Furthermore, Shuurs, et al. do not teach or suggest the determination of the concentration of TSH in a sample and comparison of the concentration of TSH with a urinary concentration of TSH in a normal subject in order to diagnose hypothyroidism or hyperthyroidism in the subject.

In light of these teachings and their shortcomings, the Examiner has failed to show how the cited references teach or suggest every element of the claimed invention, or create a motivation to combine or a reasonable expectation of success.

Accordingly, the Examiner has failed to establish the *prima facie* obviousness of claims 94-101, 132 and 133 over Kuku, et al. and Shuurs, et al.

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The Examiner also rejected claims 110-122 and 134 under 35 U.S.C. §103(a) as allegedly unpatentable over Kuku, et al., in view of Shuurs, et al. and Philo, et al. (U.S. Patent No. 5,108,896).

In response to the Examiner's rejection, applicants respectfully traverse, and maintain that the Examiner has failed to establish a *prima facie* case of obviousness.

To support a *prima facie* case of obviousness, one of ordinary skill would have had to be motivated to combine the teachings of Kuku, et al., in view of Shuurs, et al. and Philo, et al. at the time of the invention. Also, these references would have had to provide a reasonable expectation of success. The cited combination of references, however, fails to do this.

Claims 110-122 and 134 provide a method of diagnosing a thyroid condition in a subject. This method comprises obtaining a suitable urine sample from the subject, determining the concentration of TSH and the concentration of thyroxine in the sample by a method which is not a radioimmunoassay and comparing the concentration of TSH with a urinary concentration of TSH in a normal subject and comparing the concentration of thyroxine with a urinary concentration of thyroxine in a normal subject. In this method, (i) a concentration of TSH which is higher than the urinary concentration of TSH in the normal subject and a concentration of thyroxine which is lower than the urinary concentration of thyroxine in the normal subject diagnoses hypothyroidism in the subject and (ii) a concentration of TSH which is lower than the urinary concentration of TSH in the

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normal subject and a concentration of thyroxine which is higher than the urinary concentration of thyroxine in the normal subject diagnoses hyperthyroidism in the subject.

Kuku, et al. and Shuurs, et al. are discussed above. Again, these references do not teach or suggest the diagnosis of a thyroid condition in a subject, especially one which comprises obtaining a suitable urine sample from the subject. Furthermore, these references do not teach the determination of the concentration of TSH in a sample and comparison of the concentration of TSH with a urinary concentration of TSH in a normal subject in order to diagnose hypothyroidism or hyperthyroidism in the subject.

Philo, et al. fail to cure the deficiencies of Kuku, et al. and Shuurs, et al. Philo, et al. teach dual analyte enzyme immunoassays for assaying two antigens in a single liquid sample wherein the two immunoreactions are carried out simultaneously. According to Philo, et al., the antigen pair can be, for example, TSH and thyroxine.

Philo, et al. do nothing more than provide a general analytical method using antibodies. Neither Philo, et al. alone, nor in combination with the other cited references, provide an impetus for using this antibody method in connection with a diagnostic method of the type claimed.

Accordingly, the Examiner has failed to establish the *prima facie* obviousness of claims 110-122 and 134 over Kuku, et al., in view of Shuurs, et al. and Philo, et al. For the same

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reasons, applicants alternatively maintain that the rejected claims would not have been obvious over these references.

In view of the above remarks, applicants maintain that claims 94-101, 110-122 and 132-134 satisfy the requirements of 35 U.S.C. §103(a).

Summary

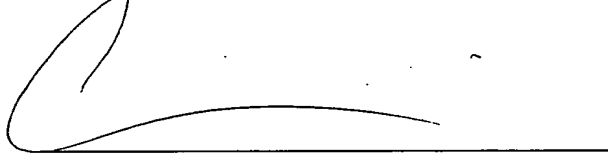
In view of the foregoing remarks, applicants respectfully request that the above grounds of rejection be reconsidered and withdrawn and earnestly solicit allowance of the pending claims.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.

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No fee is deemed necessary in connection with the filing of this Communication. However, if any fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,



I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:

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